Side Effects from the Pulsed Dye Laser: The Importance of Skin Pigmentation and Skin Redness

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The pulsed dye laser is the treatment of choice for port-wine stains. In this study we evaluate the importance of preoperative skin pigmentation and skin redness for the development of side effects from one treatment with the pulsed dye laser. A risk assessment is performed and skin reflectance measurement objectifies postoperative pigmentary changes. Fourteen human volunteers (skin types I to V) were laser-treated on the inside of the proximal brachium. Photographic documentation was used for blinded, clinical evaluation of side effects 3 and 6 months postoperatively. Skin was artificially reddened using topical application of 10% nicotinic acid cream. The development of pigmentary alterations and texture changes depended on the preoperative pigmentation and redness degrees. The risk of inducing clinically visible pigmentary alterations and texture changes increased with higher preoperative skin pigmentation and redness degrees, and with the application of increasing laser doses. Pigmentary alterations were induced at a lower fluence level than texture changes. The risk of side effects was higher 3 months postoperatively than 6 months postoperatively, substantiating a gradual disappearance of side effects. Skin reflectance measurements documented postoperative hyperpigmentation that faded partially from 3 to 6 months postoperatively.

This is the first human experimental model for port-wine stains which provides quantitative data on the relationship between preoperative skin colours and postoperative clinically disturbing side effects. *Key words: Cicatrix; experimental study; hyperpigmentation; hypopigmentation.*

The pulsed dye laser (PDL) has become established as the treatment of choice for port-wine stains (PWS) in the paediatric population (1, 2). In general, half of the children achieve about 75% blanching after two to three treatments (1, 3). The degree of blanching is, however, unpredictable for the individual child, since an indefinable subgroup of children responds slowly and with a poor outcome (4, 5).

An overall satisfactory treatment outcome and cosmetic end result requires a high degree of blanching together with a low occurrence of side effects. The incidence of adverse reactions is generally considered low for the PDL in the treatment of PWS (4, 6–9). Nevertheless, clinical studies have recently outlined that the incidences of scarring and pigmentary alterations are higher than previously reported (10, 11); atrophic scarring occurring in 3–4% of the treated patients and hyperpigmenta-tion in 9–27%. Consequently, there is concern about the occur-rence of side effects from PDL treatment of patients with PWS.

It is well known that the vessel specificity of the PDL decreases with increasing skin pigmentation (12, 13) and it is well established that persons with dark complexions are at higher risk of having side effects than fair-skinned persons after treatment of vascular lesions (14, 15). The preoperative redness degree has been associated with the final treatment outcome (9, 16), whereas the relation to the development of side effects has not so far been examined.

The present study examines the importance of preoperative skin pigmentation and skin redness for the development of pig-mentary changes and texture changes 3 and 6 months after one treatment with the PDL. The results are used to calculate the risk of inducing side effects for skin with different preoperative pigmentation and redness degrees. Moreover, skin reflectance measurement objectifies laser-induced pigmentary alterations.

MATERIAL AND METHODS

Patients and experimental design

Fourteen healthy, human volunteers (5 females, 9 males aged 21–48 years, mean age 28 years) were enrolled in the study after the nature of the procedures had been fully explained and informed consent was obtained. Skin types ranged from type I to type V according to the Fitzpatrick skin type classification system (17) (one volunteer had skin type I, three type II, seven skin type IV and three type V). None were tanned due to sun exposure or use of sunbeds. Laser treatment was performed in three rectangular test regions on the inside of the proximal brachium; (i) normal skin, (ii) reddened skin, pretreated with 10% nicotinic acid (NA) cream, and (iii) skin pretreated with placebo cream. No local anaesthesia was used. Preoperatively, skin pigmen-tation and skin redness were quantified by means of skin reflectance measurements (18). Clinically visible side effects were assessed 3 and 6 months postoperatively by blinded, photographic evaluations. Reflectance measurements quantified laser-induced pigmentary changes.

Laser equipment

A commercially available flashlamp-pumped PDL (Candela SPTL-1b, Candela Corp., Wayland, Mass., USA) with a wavelength of 585 nm ± 5 nm and a pulse duration of 450 µs was used. Five laser fluences were applied to each of the three test regions; each fluence was delivered in test areas (1.44 cm^2) consisting of four slightly overlapping pulses with a spot diameter of 7 mm. The energy fluences ranged between 3 and 8 J/cm^2, with 1 J/cm^2 increments; the applied fluences depended on the degree of skin pigmentation; in general, darker complected volunteers were treated with the lowest energy densities. An external pyoelectric energy meter (Ophir PE50-DIF) calibrated to ± 3% was used to moni-tor fluences.

Creams

The NA cream and the placebo cream were produced at the pharmacy of the National University Hospital in Copenhagen. The placebo

Table I. *The clinical score system used 3 and 6 months postoperatively to quantify laser-induced pigmentary alterations and laser-induced texture changes*

Score	Pigmentary alterations	Texture changes
0	No visible changes or just visible blanching	No visible changes
1	Just visible, diffuse hyperpigmentation	Shiny epidermal appearance
2	Slight hyperpigmentation	Cigarette-paper-like texture change with alterated, but preserved, skin folds. Changes constitute ≤ 50% of the treatment area
3	Moderate hyperpigmentation	Cigarette-paper-like texture change with altered, but preserved, skin folds. Changes constitute > 50% of the treatment area
4	Intense hyperpigmentation in the entire treatment area, possibly with clear border hyperpigmentation	Slightly atrophic scarring constituting ≤ 50% of the treatment area. Atrophy is defined as absence of normal skin pattern/folds
5	Heavy hyperpigmentation exceeding the treatment area, or spotted depigmented areas/hypopigmentation in combination with hyperpigmentation	Moderately atrophic scarring constituting > 50% of the treatment area. Atrophy is defined as absence of normal skin pattern/folds
6	Moderate hypopigmentation in most of the treatment area; perhaps combined with areas of hyperpigmentation in the treatment area	Hypertrophic scarring
7	Intense hypopigmentation in the entire treatment area. No hyperpigmentation IN the treatment area but perhaps hyperpigmentation OUTSIDE the treatment area	Marked scarring (atrophic or hypertrophic) exceeding the treatment area

cream contained 0.5% polysorbate 80, 5% cetylane, 5% paraffin oil, 6% glycerolmonostearate 40–50, 4% glycerol 85%, 7% sorbitol and purified water to 100%. The 10% NA cream was produced on the basis of the placebo cream. The two test creams were applied evenly to the test regions in an amount of 3 mg/cm^2. Laser exposure was initiated at 30–60 min after application of the creams; the time interval depending on the time to erythemal reaction. However, two volunteers responded slowly to the NA cream; erythema being maximal 23 and 26 h after application and, consequently, for these two individuals the laser treatments were performed at that interval.

Evaluation of side effects

Clinical evaluation of side effects was performed blinded by a trained laser assistant 3 and 6 months postoperatively from photographic documentation. Scoring of laser-induced pigmentary alterations and texture changes was based on the classification given in Table I. All photographs were obtained under standardized conditions as previously described (19). Skin reflectance measurements quantified pigmentary alterations 3 and 6 months postoperatively (UV-Optimize, Matic, Herlev, Denmark). The method has been described extensively (18, 19).

Statistics

The clinical data were analysed using ordinal logistic regression, which describes the risk of inducing side effects after laser therapy as a mathematical function of the risk variables in the model, i.e. preoperative skin pigmentation, preoperative skin redness and laser fluence. The logistic regression took into consideration the inter- and intraindividual variation. The statistical computing package was "SAS ®", version 6.11, PROC LOGISTIC". The skin reflectance data were presented and analysed by means of non-parametric statistics. Consequently, medians with 25th and 75th percentiles are given for descriptive statistics. The Friedman's two-way analysis of variance and the Wilcoxon rank sum test were used for paired comparisons; these were based on median values from each volunteer. Correlations were described with the Spearmann correlation coefficients and their corresponding *p* values. The *p* values were considered significant at $p \leq 0.05$.

RESULTS

Results are presented on (i) degrees of preoperative skin pigmentation and redness determined by skin reflectance, (ii) clinical occurrence of side effects, (iii) risk assessment of side effects from laser treatment of skin with different degrees of preoperative pigmentation and redness, and (iv) pigmentary changes objectified by skin reflectance.

Preoperative skin pigmentation and redness determined by skin reflectance

Preoperative skin pigmentation ranged from 11% to 74%. The median values (with 25th and 75th percentiles) were 24% (18–35%) in the normal skin test region, 26.5% (21–37.5%) in the placebo cream test region, and 24% (18–34%) in the NA-treated test region. Preoperative redness ranged from 0% to 31%. The median values were (with 25th and 75th percentiles) 13.5% (10–18%) in the normal skin test region, 10% (2–14%) in the placebo cream test region, and significantly higher in the NA-treated test region 20.5% (14–26%) ($p < 0.01$).

Clinical occurrence of side effects

Pigmentary alterations and texture changes included a broad range of skin reactions from subtle, diffuse hyperpigmentation and shiny epidermal appearance to hyperpigmentation exceeding the treatment area, hypopigmentation in the majority of the treatment area, or atrophic scarring in the treatment area. No hypertrophic scarring was observed. Generally, the frequencies of side effects decreased from 3 to 6 months postoperatively and pigmentary alterations occurred more frequently than texture changes (frequencies not shown). The clinical scores 6 months postoperatively depended on the preoperative pigmentation degree and, moreover, the NA-reddened test region obtained significantly higher scores of
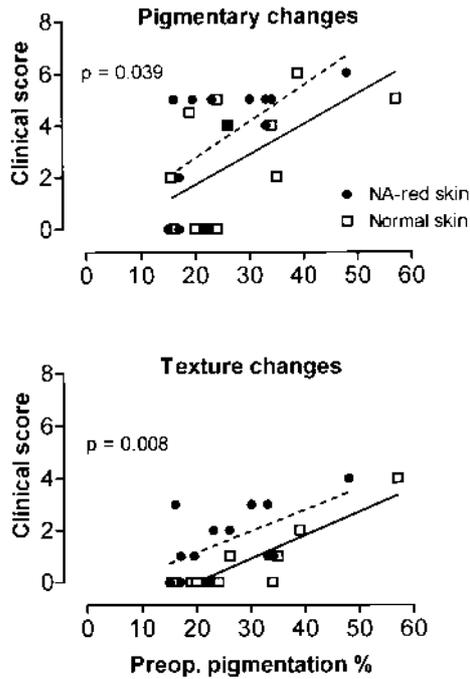
Fig. 1. The 6-month postoperative clinical scores of pigmentary changes and texture changes (7 J/cm^2) versus preoperative pigmentation. Results are shown for two test regions: Nicotinic acid (NA) red skin (● and dotted trend line) and normal skin (□ and solid trend line). The *p* values refer to significance levels for comparisons between the two test regions; NA red skin obtained significantly higher clinical scores than the normal skin. Preoperative pigmentation percentages were similar within these test regions. The Spearman's correlation coefficients with corresponding *p* values in parentheses were: *Pigmentary changes* 0.59 ($p = 0.034$) NA red skin, 0.60 ($p = 0.032$) normal skin. *Texture changes:* 0.50 ($p = 0.085$) NA red skin, 0.78 ($p = 0.002$) normal skin. Trends are shown to illustrate the correlation coefficients, although the y-axis variable does not represent continuous data.

Fig. 2. Contour lines are illustrated for given risks of inducing pigmentary changes and texture changes 6 months after laser exposure of 7 J/cm^2. The contour lines represent combinations of preoperative pigmentation and redness percentages, which result in given risk levels of 1, 2, 5, 10, 20 and 50% to induce just visible, diffuse hyperpigmentation (pigmentary changes, score 1) and shiny epidermal appearance (texture changes, score 1). Similar contour lines were obtained for other fluence levels than 7 J/cm^2; increasing fluence levels deviating increasingly to the left.

pigmentary changes and texture changes than the normal skin test region (Fig. 1, 7 J/cm^2). Similar tendencies were found 3 and 6 months postoperatively for other fluence levels than 7 J/cm^2.

Risk assessment of clinically evaluated side effects

The ordinal logistic regression analyses demonstrated that laser fluence, preoperative skin pigmentation and preoperative skin redness were significant risk factors for the induction of pigmentary and texture changes 3 and 6 months postoperatively. The placebo cream *per se* had no influence on the risk of side effects.

The risk of inducing just visible, diffuse hyperpigmentation and a shiny epidermal appearance 6 months after laser treatment of skin with different degrees of preoperative pigmentation and redness is illustrated graphically in (7 J/cm^2, Fig. 2). It is seen that the risk of inducing side effects increases with increasing preoperative pigmentation and redness percentages (Fig. 2). The contour lines for fluence levels of 3, 4, 5, 6, 7 and 8 J/cm^2 had similar appearances, increasing fluence levels deviating increasingly to the left (not shown). This finding indicates that application of increasing laser fluences
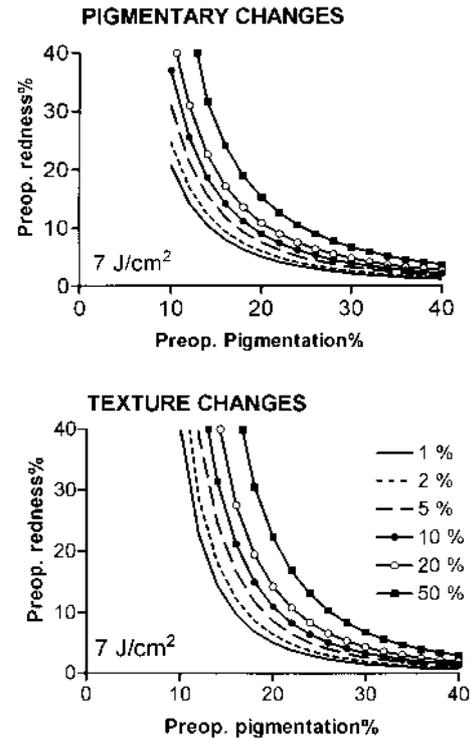
increases the risk of inducing side effects. For instance, an individual with 15% preoperative pigmentation and 40% preoperative redness has a 1% risk of obtaining a shiny epidermal appearance 6 months after treatment with 5 J/cm^2, 10% risk after treatment with 6 J/cm^2, 20% risk after treatment with 7 J/cm^2, and 50% risk after treatment with a fluence of 8 J/cm^2. Compared with the 6-month contour lines, the 3-month contour lines to produce pigmentary alterations and texture changes were similar but deviated to the left (not shown). There is, therefore, a higher risk of side effects 3 months postoperatively than 6 months postoperatively for individuals treated with identical laser fluences and having identical degrees of preoperative skin pigmentation and redness, indicating a gradual disappearance of the side effects from 3 to 6 months postoperatively. For instance, an individual with 13% preoperative pigmentation and 30% preoperative redness has a 10% risk of obtaining a shiny epidermal appearance 3 months after laser treatment (7 J/cm^2), whereas 6 months postoperatively the risk is reduced to 5%. Pigmentary changes were induced at a lower fluence level than texture changes for skin with identical preoperative pigmentation and redness degrees. For instance, an individual with 10% preoperative pigmentation and 30% redness has less than a 1% risk of texture changes, whereas 6 months after
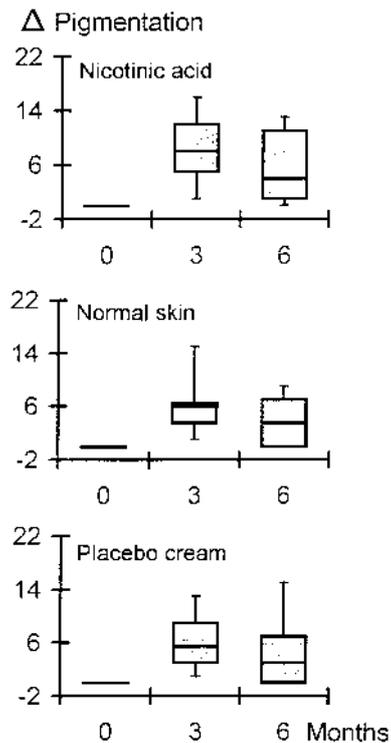
Δ Pigmentation

Fig. 3. Skin reflectance-evaluated hyperpigmentation 0, 3 and 6 months postoperatively within the three test regions at a fluence level of 6 J/cm^2. Hypopigmented test areas were excluded in order to avoid counteractive pigmentary changes. The same trend was observed for other treatment fluences than 6 J/cm^2. The box extends from the 25th percentile to the 75th percentile, with a horizontal line at the median (50th percentile). Whiskers show the range of the data.

laser treatment with 7 J/cm^2 the risk of pigmentary changes is 5% (Fig. 2).

Pigmentary changes objectified by skin reflectance

The pigmentation was corrected for acquired variations in skin pigmentation due to sun exposure during the observation period by subtracting the pigmentation of the corresponding untreated control test area. At fluences higher than 4 J/cm^2 these corrected pigmentation percentages were significantly higher 3 and 6 months after laser exposure than before within the three test regions (Fig. 3, $p < 0.05$). The laser-induced hyperpigmentation decreased from 3 to 6 months postoperatively but did not fade to the preoperative level. Hyperpigmentation was more intense in the NA-reddened skin than in normal and placebo cream skin areas (Fig. 3, 3 months postoperatively: $p < 0.05$; 6 months postoperatively: $p = $ns). No postinflammatory hyperpigmentation was seen in the control area in the NA test region. No differences were seen between the normal skin and the placebo cream treated test regions ($p = $ns). Significant correlations were seen within the three test regions between the applied laser doses and the degree of hyperpigmentation 3 and 6 months postoperatively (r values between 0.29 and 0.64, $p < 0.03$; correlations were generally highest at the 3 months' assessments). No correlation was seen between preoperative redness percentage and the degree of postoperative hyperpigmentation, whereas the correlation between preoperative skin pigmentation and the degree

of laser-induced hyperpigmentation occasionally was significant .

DISCUSSION

It is well known that NA causes cutaneous erythema due to vasodilatation (20, 21). This knowledge has constituted the basis of our study, in which we have laser-treated human volunteers with different complexions ranging from skin types I – V. Using this model, we evaluated the importance of two influential parameters, constitutional skin pigmentation and skin redness, for the development of side effects from one treatment with the PDL. We found that the risk of inducing clinically visible pigmentary alterations and texture changes increased (i) with increasing constitutional skin pigmentation, (ii) with increasing degrees of preoperative redness, and (iii) with the application of increasing laser doses. This means that patients with dark complexions and red PWS may be at higher risk of obtaining side effects from the PDL than patients with fair complexions and pink PWS.

The incidence of clinically visible side effects is generally considered low for the PDL in the treatment of PWS (4, 6 – 9), although it has recently been outlined that the incidences of scarring and pigmentary alterations are higher than previously estimated (10, 11); atrophic scarring occurs in 3 – 4% of the treated patients and hyperpigmentation in 9 – 27%. The fact that minor differences in skin pigmentation and skin redness are significant risk factors for the occurrence of side effects after treatment with the PDL may account for some of the variability in the reported incidences of side effects. The risk levels of inducing pigmentary and texture changes reported here were higher than expected from the reported frequencies of side effects in the literature. The frequent occurrence of side effects in our study may be explained by several conditions: (i) The clinical photos were examined for even the slightest visible side effects, (ii) about half of the included volunteers had a high risk of inducing side effects (seven volunteers with skin type IV, three with skin type V), and (iii) fluences were used up to 8 J/cm^2 that represent relatively high fluences when applied with a 7 mm spot size. The high fluence levels were included to cover a broad spectrum of clinically visible side effects, which is essential in a study dealing with side effects. However, in order to minimize the cosmetic inconvenience to the volunteers, the test areas were located at the inside of the upper arm, although this region is not a common location for capillary malformations.

We found that laser-induced pigmentary alterations were provoked at a lower fluence level than texture changes for individuals with identical degrees of preoperative pigmentation and redness, indicating that hyperpigmentation may be the first sign that the laser fluence used has been too high. However, an individual predisposition to hyperpigmentation, and external factors such as UV exposure, hormone therapy, and infection, may also provoke the synthesis of melanin, and hyperpigmentation may therefore not solely be explained by a high laser fluence. We consider these factors of minor importance in this study.

We found, furthermore, that the risk of inducing side effects was higher 3 months after laser treatment than 6 months after treatment, suggesting a gradual disappearance of the clinical side effects. These results were confirmed by the objective skin reflectance measurements, which documented that the laser-

induced hyperpigmentation fades from 3 to 6 months after the laser treatment but does not return to the preoperative level at the end of this observation period. Unfortunately, the reflectance measurements are not able to differentiate between melanin and hemosiderin-induced pigmentation, which might have provided useful information. Nevertheless, the fading is in accordance with previous clinical studies having reported the laser-induced hyperpigmentation to be transient (3, 10, 22).

This is not the first study emphasizing the importance of skin pigmentation. It has previously been documented that the epidermal melanin represents an overlying, competitive chromophore through which the laser beam must pass in order to target the dermal oxyhemoglobin (23). Furthermore, studies have clarified that the most specific vascular injury is obtained in skin types of fair complexion (12, 13) and a case report has described that no improvement takes place in a black patient with a PWS after treatment with the PDL, whereas persistent hypopigmentation and textural changes are induced (14). According to clinical experience, it is generally recommended that incoming patients for laser treatment use high-factor sunscreens, protecting against both UVA and UVB radiation, in order to avoid UV-induced hyperpigmentation (10, 24). Patients are also recommended not to visit solariums and not to go sunbathing, although the influence of acquired pigmentation compared with constitutional pigmentation for the development of side effects is unknown.

The degree of redness has previously been associated with treatment outcome (9, 16), whereas, to our knowledge, the importance of skin redness to the development of side effects has not been examined. We found that an increasing degree of preoperative redness was associated with a higher risk of inducing side effects. This finding corresponds to the clinical situation that laser-induced purpura is more intense in dark red lesions than in light red lesions due to a high amount of target chromophore. However, the results from this artificially reddened normal skin may not be directly comparable with laser treatment of PWS because the vasodilatation due to the topical application of NA does not correspond to the histological appearance of the PWS that are characterized by capillary ectasia in the papillary and superficial reticular dermis (25) and sometimes by an increased blood flow (26). The NA model has the additional limitation that the degrees of redness never exceeded 31%, which is below the typical redness percentages of dark-red and purple PWS (40–55%). However, by means of a modest extrapolation, the ordinal regression model may allow a reasonably reliable prediction of the importance of degrees of redness up to about 40%, thereby resembling laser treatment of light-red and red PWS. Moreover, despite a limited sample size (14 volunteers), the risk levels were established with a high degree of precision, since the classification of the response into several ordered categories allows a more precise assessment of the risk levels than if responses had been based on binary response variables ($\pm$ occurrence of side effects).

This is the first human experimental model for PWS which provides quantitative data on the relationship between preoperative skin colours and postoperative clinically disturbing side effects.

ACKNOWLEDGEMENTS

REFERENCES

1. Geronemus RG. Pulsed dye laser treatment of vascular lesions in children. J Dermatol Surg Oncol 1993; 19: 303–310.
2. Spicer MS, Goldberg DJ. Lasers in dermatology. J Am Acad Dermatol 1996; 34: 1–25.
3. Reyes BA, Geronemus RG. Treatment of port-wine stains during childhood with the flashlamp-pumped pulsed dye laser. J Am Acad Dermatol 1990; 23: 1142–1148.
4. Kauvar AB, Geronemus RG. Repetitive pulsed dye laser treatments improve persistent port-wine stains. Dermatol Surg 1995; 21: 515–521.
5. Troilius A, Ljunggren B. Reflectance spectrophotometry in the objective assessment of dye laser-treated port-wine stains. Br J Dermatol 1995; 132: 245–250.
6. Levine VJ, Geronemus RG. Adverse effects associated with the 577- and 585-nanometer pulsed dye laser in the treatment of cutaneous vascular lesions: a study of 500 patients. J Am Acad Dermatol 1995; 32: 613–617.
7. Alster TS, Wilson F. Treatment of port-wine stains with the flashlamp-pumped pulsed dye laser: extended clinical experience in children and adults. Ann Plast Surg 1994; 32: 478–484.
8. Ashinoff R, Geronemus RG. Flashlamp-pumped pulsed dye laser for port-wine stains in infancy: earlier versus later treatment. J Am Acad Dermatol 1991; 24: 467–472.
9. Fitzpatrick RE, Lowe NJ, Goldman MP, Borden H, Behr KL, Ruiz-Esparza J. Flashlamp-pumped pulsed dye laser treatment of port-wine stains. J Dermatol Surg Oncol 1994; 20: 743–748.
10. Seukeran DC, Pollis P, Sheehan-Dare RA. Adverse reactions following pulsed tunable dye laser treatment of port wine stains in 701 patients. Br J Dermatol 1997; 136: 725–729.
11. Wlotzke U, Hohenleutner U, Abd El-Rahem T, Baümler W, Landthaler M. Side-effects and complications of flashlamp-pumped pulsed dye laser therapy of port-wine stains. A prospective study. Br J Dermatol 1996; 134: 475–480.
12. Tan OT, Kerschmann R, Parrish JA. The effect of epidermal pigmentation on selective vascular effects of pulsed laser. Lasers Surg Med 1984; 4: 365–374.
13. Tong AKF, Tan OT, Boll J, Parrish JA, Murphy GF. Ultrastructure: effects of melanin pigment on target specificity using a pulsed dye laser (577 nm). J Invest Dermatol 1987; 88: 747–752.
14. Ashinoff R, Geronemus RG. Treatment of a port wine stain in a black patient with the pulsed dye laser. J Dermatol Surg Oncol 1992; 18: 147–148.
15. Hœdersdal M, Wulf HC. Pigmentation dependent side effects to copper vapor laser and argon laser treatment. Lasers Surg Med 1995; 16: 351–358.
16. Fiskerstrand EJ, Svaasand LO, Kopstad G, Dalaker M, Norvang LT, Volden G. Laser treatment of port wine stains: therapeutic outcome in relation to morphological parameters. Br J Dermatol 1996; 134: 1039–1043.
17. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 1988; 124: 869–871.
18. Wulf HC. A method and an apparatus for determining an individual's ability to stand exposure to ultraviolet radiation prior to erythema. Patent application US. 4,882,598. 1986.
19. Hœdersdal M, Efsen J, Gniadecka M, Fogh H, Keiding J, Wulf HC. Changes in skin redness, pigmentation, echostructure, thickness, and surface contour after 1 pulsed dye laser treatment of port-wine stains in children. Arch Dermatol 1998; 134: 175–181.

20. Morrow JD, Parsons WG, Roberts LJ. Release of markedly increased quantities of prostaglandin D_2 in vivo in humans following the administration of nicotinic acid. Prostaglandins 1989; 38: 263–274.

21. Wilkin JK, Fortner G, Reinhart LA, Flowers OV, Kilpatrick SJ, Streeter WC. Prostaglandins and nicotinate-provoked increase in cutaneous blood flow. Clin Pharmacol Ther 1985; 38: 273–277.

22. Garden JM, Polla LL, Tan OT. The treatment of port-wine stains by the pulsed dye laser. Analysis of pulse duration and long-term therapy. Arch Dermatol 1988; 124: 889–896.

23. Anderson RR, Parrish JA. The optics of human skin. J Invest Dermatol 1981; 77: 13–19.

24. Pickering JW, Walker EP, Butler PH, van Halewyn CN. Copper vapour laser treatment of port-wine stains and other vascular malformations. Br J Plast Surg 1990; 43: 273–282.

25. Dover JS, Jackson BA, Junkins-Hopkins JM, Arndt KA, Robinson JK, LeBoit PE, et al. What benign and malignant proliferations of cells affect the skin, and how are they treated? In: Pocket guide to cutaneous medicine and surgery. Philadelphia: W. B. Saunders, 1996: 532–636.

26. Troilius A, Wardell K, Bornmyr S, Nilsson GE, Ljunggren B. Evaluation of port wine stain perfusion by laser Doppler imaging and thermography before and after argon laser treatment. Acta Derm Venereol (Stockh) 1992; 72: 6–10.